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Chemoradiotherapy for advanced lymphoepithelioma-like carcinoma of the lung

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Lymphoepithelioma-like carcinoma (LELC) of the lung, an Epstein–Barr virus-associated undifferentiated carcinoma, is a rare entity of pulmonary malignancy. It tends to affect young non-smoking Asians and is often resectable. However, little is known of the treatment of the even rarer locally advanced or metastatic cases. We report our experience of three Chinese patients with advanced LELC of the lung who were treated with combination-chemotherapy (5-fluorouracil, leucovorin, and cisplatin) and radiotherapy. The encouraging response of these patients supports the use of this regime in other patients

Key words: lymphoepithelioma; chemotherapy; radiotherapy.

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Introduction

Begin *et al*. first reported lymphoepithelioma-like carcinoma (LELC) of the lung in 1987 (1). LELC of the lung tends to affect young non-smoking patients and the mean age of affected patients has been reported to be 10 years less than that of other histological types of non-small cell lung carcinoma in a Taiwanese series (2–4, 8). The mean age was 48 years in a Hong Kong series (3). There are only about 30 reported cases in the current literature and three of the major series were reported from Hong Kong (2–4). Some studies, largely retrospective pathological series, on the epidemiology, histopathology and association with Epstein–Barr virus (EBV) have been reported (2,3,5–12). It is interesting that, despite being a true neoplasm, metastatic spreading of LELC is considered exceptionally rare (1–5). The treatment of LELC is controversial and there has been no consensus. There has only been one report on induction chemotherapy (13), another on postoperative chemotherapy (6), and a few case reports of postoperative radiotherapy for this rare condition (5,7). For advanced LELC of the lung, there was only one reported series in the use of chemoradiotherapy as the primary form of treatment (4).

We have prospectively studied the effects of systemic chemotherapy and local radiotherapy in our series of patients with advanced stage LELC of the lung. Our experience and this treatment regime should provide insight into the treatment of this rare form of pulmonary malignancy.

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Methods

Our centre is a tertiary respiratory referral centre for treatment of patients with non-small cell carcinoma of the lung in Hong Kong. Routine investigations performed to confirm the diagnosis for these patients include chest radiography, computed tomography (CT) of the thorax and fibre-optic bronchoscopy. Tissue biopsy was obtained and always reviewed by a specialist pulmonary pathologist. In the presence of histological evidence of LELC of the lung, serum IgA titre for EBV, *in situ* hybridization (ISH) for EBV-encoded small nuclear RNA (EBER), endoscopic examination and biopsy of nasopharynx, and magnetic resonance imaging (MRI) of the nasopharynx were performed to exclude nasopharyngeal carcinoma which is a common EBV-associated cancer in Hong Kong and south China. Serum IgG levels against the viral capsid antigen (VCA) of Epstein–Barr virus was determined by using routine established methodology at the Clinical Microbiology Laboratory of the University of Hong Kong. Briefly, IgG against Epstein–Barr VCA was determined by immunofluorescent technique using fluorescein–isothiocyanate-conjugated and heavy chain-specific goat anti-human sera (Dako, Denmark). Titres were expressed as the reciprocal of the maximum dilution, which gave a positive immunofluorescence as described previously (14). ISH for EBER was performed on representative paraffin sections of tumours as described previously (3). Very briefly, digoxigenin-labelled anti-sense riboprobes were generated by *in*

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TABLE 1. Patients characteristics and other clinical details

Patient no.	Gender	Age (years)	Smoke	Performance state (WHO)	Presenting symptom	Biopsy site	EBER	Stage	Metastatic sites	Response to chemotherapy	RT	Response to RT	Survival* (months)
1	M	47	Yes	0	cough	LN	+ve	3B	LN	NC	Yes	PR	13
2	F	39	No	0	cough	lung	+ve	4	LN, bone	PR	No	NA	5
3	F	38	No	0	cough, haemoptysis	lung	NA	4	LN, lung	PR	No	NA	4

IgA VCA: immunoglobulin A to EBV viral capsid antigen; EBER: EBV-encoded small nuclear RNA; RT: radiotherapy; LN: lymph node; NA: not applicable; PR: partial response; NC: no change.
*Survival: from presentation to the time of writing, all surviving at the time of writing.

vitro transcription from a Bluescript vector containing the EBER 1 and 2 genes of the virus. Hybridization signal was detected by standard immunohistochemical methods, using anti-digoxigenin monoclonal antibody, biotinylated secondary antibody, and streptavidin–alkaline phosphatase complex. Two of our three patients had sufficient biopsy material for ISH, which was positive in both cases.

Chemotherapy for lung LELC constituted four 4-weekly cycles of 5-fluorouracil (5-FU, $1000\,mg\,m^{-2}\,day^{-1}$ on day 1 to 4), leucovorin ($200\,mg\,m^{-2}$ on day 1 to 4), and cisplatin ($100\,mg\,m^{-2}$ on day 1). Sequential local radiotherapy to mediastinum, given as $16 \times 2{\cdot}5\,Gy$/fraction, was included for locally advanced disease. Tumour response was assessed by thoracic computed tomography. Adverse effects from chemotherapy were recorded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC).

Results

Three cases (two females, mean age 42 years) of lung LELC were recruited between July 1998 and June 1999. The baseline characteristics of the patients are presented in Table 1. Two were never-smokers and one patient was a smoker. All cases were in good performance state (WHO 0). Serum IgA titres to EBV were raised to the upper limit of detection of our laboratory at $> 1/640$ in all three cases. These remained at the same level throughout the course of chemotherapy. Two of the patients had adequate biopsy specimens for detection of EBER which were positive (Fig. 1). All three patients were given the above standard chemotherapy (5-FU, leucovorin, and cisplatin) and one patient was also given sequential radiotherapy. After four courses of chemotherapy, two patients achieved a partial response with $> 50\%$ reduction in tumour size on thoracic CT scanning (Fig. 2). The remaining patient had an unaltered volume of tumour despite chemotherapy and was given mediastinal radiotherapy 40 Gy (2·5 Gy/fraction for 16 days) which led to a partial response. The chemotherapy regimes were well tolerated except for moderately severe vomiting (Table 2). There were no life-threatening complications. Marked symptomatic palliation occurred in all three cases. At the time of writing, the three patients have remained asymptomatic and survived for 13, 5 and 4 months from presentation.

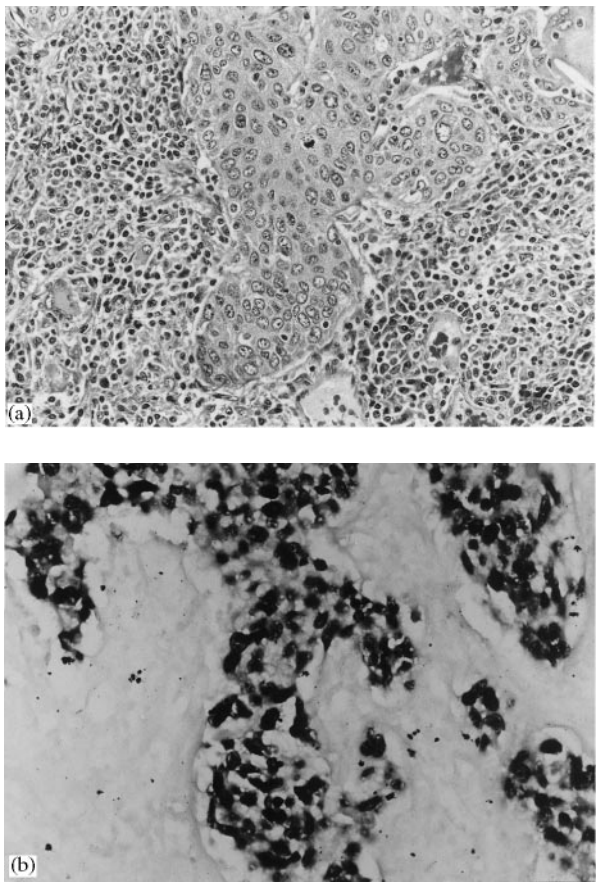

FIG. 1. Photomicrograph obtained for patient 1 showing (a) irregular islands of tumour cells in a stroma bearing numerous inflammatory cells. The tumour cells showed squamoid features but keratinization or intercellular bridges were absent (H&E, × 250); and (b) *in situ* hybridization for EBER showed strong hybridization signals in all tumour cells but the stroma remained negative (antisense probe for EBER, × 200)

Discussion

Our series of three cases presented with cough or haemoptysis in which histological proof of LELC was obtained by lung or lymph node biopsy. Nasopharyngoscopic biopsy and

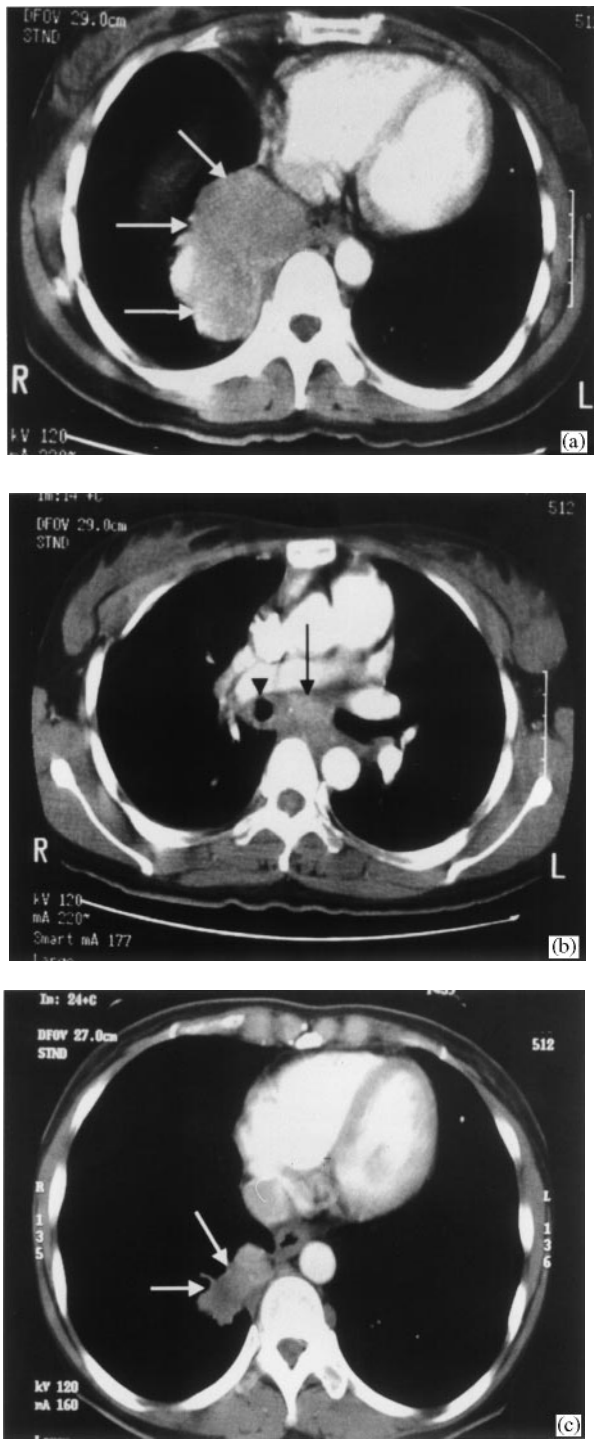

FIG. 2. Thoracic computed tomography (CT) of one of the patients showing (a) a $2 \times 2 \times 5$ cm^3 lower lobe tumour and (b) mediastinal lymphadenopathy (arrow) before treatment with 5-fluorouracil, leucovorin and cisplatin; and (c) the reduction in tumour bulk after chemotherapy.

magnetic resonance imaging excluded nasopharyneal carcinoma. The chemotherapy regime, namely a combination of 5-flurouracil, leucovorin and cisplatin, was effective in shrinking the tumour bulk leading to partial response in two of the three cases. Sequential radiotherapy in the remaining case achieved partial response. The good efficacy of our chemotherapy regime was not accompanied by significant adverse reactions.

Lymphoepithelioma-like carcinoma is an undifferentiated carcinoma associated with a prominent component of reactive lymphocytes, macrophages and plasma cells. The neoplastic cells have syncytial appearance, vesicular chromatin, distinct nucleoli and occasional spindle cell growth (2). Some may show differentiated squamoid features without cellular keratinization or intercellular bridge formation, and rarely focal glandular arrangement (3). Primary LELC of the lung is histologically indistinguishable from the prototypical LELC occurring in the nasopharynx (2). Therefore, a high index of suspicion by experienced pulmonary pathologists is required to diagnose this rare condition which is often done pathologically. Although our patients were symptomatic on presentation, most of the reported cases were detected on incidental chest radiographs (1,2,4–7,9,10,12–14). Major differential diagnoses for LELC are non-Hodgkin's lymphoma and metastatic nasopharyngeal carcinoma, both of which are common among the Chinese (5). Immunohistochemical staining helps to differentiate lymphoma from LELC (15). Endoscopic examination and random biopsies of nasopharynx, together with computed tomography or preferably magnetic resonance imaging, are often necessary to exclude primary nasopharyngeal carcinoma.

Epstein–Barr virus is associated consistently with LELC from four anatomic sites, namely, stomach, salivary gland, lung and thymus. The association of EBV with LELC of the salivary gland and lung is restricted to Asian patients, whereas the association of EBV with gastric and thymic LELC does not appear to have ethnic predisposition (16). The methods for detection of EBV in LELC include polymerase chain reaction for EBV DNA, *in situ* hybridization for EBV DNA and RNA, and immunohistochemistry for EBV-associated protein (3,12,17). The hypothesis of EBV infection preceding the clonal expansion of LELC has been substantiated by Southern-blot analysis for the presence of episomal EBV in the tumour tissue (18). Our cases demonstrate elevated serum titre for EBV-VCA IgA and positive ISH for EBER in the tumour cells, which are consistent with previous reports among Asians. However, the serum titre for EBV-VCA IgA remained elevated despite response to chemotherapy or radiotherapy in all three cases.

The few available case reports appear to suggest that LELC of the lung may be curable by resection, which is the recommended treatment of choice. In one series of five cases of resectable LELC, all survived at the time of writing, three for longer than 60 months, one 45 months, and one 38 months after surgery (9). In some cases, postoperative radiotherapy was also given (1,5,7). Postoperative chemotherapy with four cycles of carboplatinum and VP-16 had been used for stage II LELC of the lung in one report (6). There was one report of the use of induction chemotherapy consisting of 5-fluorouracil,

TABLE 2. Adverse effects associated with administration of chemotherapy regime (5-flurouracil, leucovorin and cisplation)

Patient no.	Adverse effects (grade)					
	Neutropenia	Thrombocytopenia	Infection	Vomiting	Alopecia	Stomatitis
1	1	0	0	2	1	3
2	1	1	0	3	1	2
3	1	0	0	2	1	2

All adverse graded according to NIC common Toxicity Criteria

leucovorin and cisplatin in a child with LELC of the lung resulting in significant tumour reduction (13). In a series of advanced LELC of the lung treated with palliative chemotherapy comprised of 5-fluorouracil and cisplatin, 71·4% of patients had a partial response and 28·6% had progressive disease (4). The addition of leucovorin to 5-fluorouracil, as in our chemotherapy regimen, has been shown to enhance the effect of 5-fluorouracil (19,20). As nasopharyngeal carcinoma has similar clinical and biological profiles to LELC, the response of the latter to chemotherapy regimen with 5-fluorouracil, leucovorin and cisplatin is not surprising (21). Interestingly, myelotoxicity is commonly associated with bolus administration of 5-fluorouracil and stomatitis is more frequent with prolonged continuous infusion (21). Our experience with chemoradiotherapy in the three cases showed a partial response rate of 67% (2/3) and one patient achieved a partial response to radiotherapy. The chemotherapy regime was well tolerated with no life-threatening adverse effects in our series. Based on these results, we would recommend future use of combination chemotherapy (5-FU, leucovorin and cisplatin) in advanced LELC of the lung with additional sequential radiotherapy in locally advanced disease. Newer chemotherapeutic agents, such as paclitaxel and carboplatin, have also been used in the treatment of advanced nasopharyngeal carcinoma with encouraging results (22,23). As formal clinical trials are difficult to conduct for rare diseases such as LELC, we hope advances in the management of nasopharyngeal carcinoma would further enlighten us on the treatment of LELC in the future.

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